DOI: 10.26717/BJSTR.2018.06.001339

Keti Zeka. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574-1241

Research Article | Open Access

New Resveratrol Analogues for Potential Use in Diabetes and Cancer

Keti Zeka*[1,2], Randolph RJ Arroo[2], Dritan Hasa[2], Kenneth JM Beresford[2] and Ketan C Ruparelia[2]

[1]*Department of Haematology, University of Cambridge, UK*

[2]*Faculty of Health and Life Sciences, De Montfort University, UK*

Received: June 20, 2018**; Published:** July 05, 2018

***Corresponding author:** Keti Zeka, National Health Service Blood and Transplant, Department of Haematology, University of Cambridge, Cambridge CB2 0PT, UK

Abstract

Resveratrol is a well notorious compound that may play a role in the prevention of diabetes complications and different cancers. Along, resveratrol, a naturally occurring phytoalexin, is known to exert numerous beneficial effects in the organism. Isolation of resveratrol from plants, however, has been proved being difficult. Importantly, the bioavailability in the body is poor therefore capability is reduced and not enough resveratrol reaches the target organ. In this study we generated different methoxylated resveratrol analogues using Wittig reaction. Trans stilbene obtained was 0.08 g and the *cis* one was 0.01 g. Additionally with the Horner-Witting method a yield of 0.15 g trans stilbene was obtained. By substituting the hydroxyl group with methoxy group at different positions on the aromatic rings, we could increase the efficacy and bioavailability of the Trans form of resveratrol.

Keywords: Cancer; Diabetes; Horner Wittig Reaction; Resveratrol; Stilbene; Wittig Reaction

Introduction

Diabetes is known as a chronic metabolic condition of having higher than normal blood sugar levels [1]. It involves β cells in the pancreas, which secrete a hormone called insulin. There are two types of diabetes: Type 1 and Type 2. Type 1 diabetes occurs when no insulin is being produced by the pancreas and is also known as insulin-dependent diabetes. Type 2 diabetes appears when there is relative insulin deficiency as such it increased glucose production by the liver and decreased utilization of glucose in the peripheral tissues [2]. It is well known that Type 2 diabetes can be genetically inherited and can be influenced by a number of factors such as diet, stress, alcohol consumption and lack of exercise [3]. Since the number of people diagnosed with diabetes has increased enormously, this disease is nowadays considered the 6th cause of worldwide mortality [4]. Because of the heightened aging of population and overweight people, it is estimated that by 2025 roughly 5 million people will have diabetes [4,5].

There are distinct classes of drugs which treat diabetes. Essentially, different types of insulin and as a second line treatment are the Sulphonylureas class. This class of drug cannot be taken by obese people because one of the adverse reactions is weight gain [6]. It appears clear that new treatments are urgently required to properly manage the different forms of diabetes [7-10]. Resveratrol is a stilbenoid and a phytoalexin which belongs to the large group of polyphenols found in different plant species [1]. The name stilbene (Figure 1), 1,2-diphenylethylene was derived from the Greek word stilbos, which means shining [3]. Phytoalexins are a group of phytochemicals of low molecular weight which are produced when plants are attacked by pathogens [2,3]. The richest natural source of resveratrol is *Polygonum cuspidatum* [3,5]. Also, resveratrol is synthesized in the skin cells of the grapes [11].

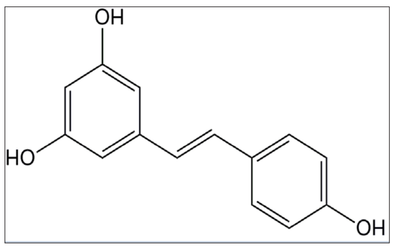

Figure 1: Structure of resveratrol

It is found 5-10% of biomass in the grape skin and absent or low in the fleshy fruit [5,11]. Trans-resveratrol is more efficient as an antioxidant than *cis*-resveratrol. However, *cis*-resveratrol has shown anti-inflammatory properties through significant modulatory effect on the nuclear factor kB related genes [9]. Nowadays, resveratrol is available in tablet form and is recommended as dietary supplement [5,10]. According to Szkudelska K et al. [5], resveratrol has calorie restriction mimetic effect which can prevent some diseases of ageing such as insulin resistance and type 2 diabetes. The proposed mechanism for this effect may be related to inducing genes for phosphorylation and mitochondrial biogenesis [5,12]. Mitochondrial biogenesis is a process when new mitochondria are formed in the cell and it is activated by many different regulators such as peroxisome proliferator activated receptor gamma (PGC-1α) during times of cellular stress. Indeed, common complications of type 2 diabetes are metabolic syndrome and oxidative stress [8-15].

Many in vitro studies [10] have tried to demonstrate resveratrol potential in both cancer initiation and progression i.e. resveratrol's can promote cell cycle arrest leading to apoptosis of tumor cells [16-19]. Moreover, the role of resveratrol in cyclooxygenese (COX) inhibition is well-known [20-24]. With the epigenetic landscape enlargement, resveratrol has been under light even more. Indeed, its capacity to reduce DNA binding activity of nuclear factor κB (NF-κB) has been proved [24-29], but a lot of investments need still to be done in term of epigenetic cancer therapies [30]. Despite its potential, there are many problems associated with resveratrol. Firstly, according to the literature, the isolation of resveratrol from plants has proved to be difficult [31,32]. In the second place, the bioavailability of resveratrol in the body is poor therefore potency is reduced and not enough resveratrol reaches the target organ [31,32].

To increase the bioavailability, resveratrol analogues with similar activity that lack the hydroxyl groups are being looked at [33,34]. Taken together these data highlight the fact that it is crucial to continue exploring the design and synthesis of resveratrol analogous. Stilbene, which the most famous derivatives is resveratrol as we mention above, is an unreactive colorless compound practically insoluble in water. There are two isomeric forms of 1,2-diphenylethylene: *trans*-stilbene, which is not sterically hindered, and *cis*-stilbene, which is sterically hindered and therefore less stable [2,35,36]. Trans-Stilbene melts around 125°C and the *cis*-stilbene melts around 6°C. From literature we know that under the influence of light trans-stilbene could isomerize to *cis*-stilbene and the reverse path can be induced by heat or light.

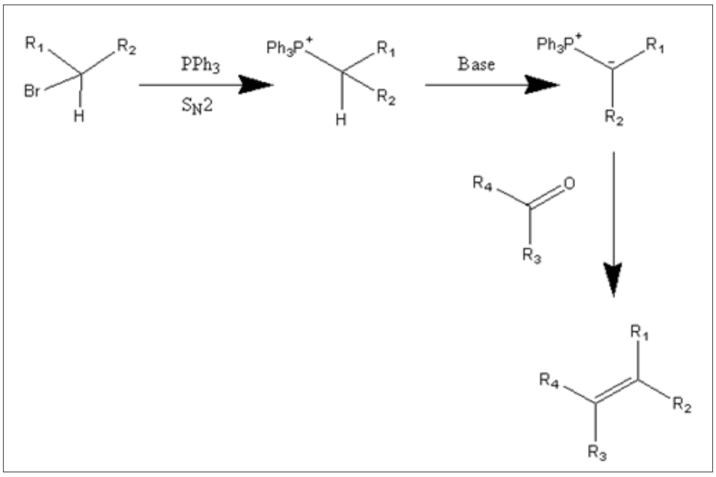

Figure 2: Wittig Reaction.

Different methods have been reported to synthesize stilbene derivatives such as Perkin reaction, Heck reaction, Aldo-type reaction, Wittig-type olefination reaction and Horner-Wittig reaction [35,36]. In this study we aim to use Wittig-type olefination reaction and demonstrate the potential to give both *cis* and *trans* isomers with an increasing yield. Wittig-type olefination reaction is used for the synthesis of alkenes [35]. The phosphorus yield, or Wittig reagent, is attacked by a carbonyl compound used as an electrophile. Addionally, to create the alkene double bond the smaller carbon units are conjoined. These interactions allow quick assemblement of molecules increased in size and complexity [35]. By increasing the stability of phosphorus yield, this will allow an increase in the Trans stilbene [36] (Figure 2).

Materials and Method

Materials

4-methoxybenzltriphenylphosphonium chloride, 3,4,5-trimethoxybenzaldehyde, n–butyllithium, anhydrous THF, ethylacetate, magnesium sulphate, 4-methoxybenzylchloride, triethylphosphite, diethyl-4-methoxybenzylphosphonate, dimethylfarmamide (DMF), sodium *tert*-butoxide, 2,4-dimethoxybenzaldehyde were supplied by Sigma Aldrich.

Chemistry

Preparation of trans and *cis*-stilbene was accomplished by means of the Wittig reaction between 3,4,5-trimenthoxybenzaldehyde and methyl-triphenyl-phosphonium chloride. 4-methoxybenzylchloride and triethylphosphite underwent Arbusov reaction to produce diethyl-4-methoxybenzylphosphonate which then was used to react with 3,4,5- trimethoxy-benzyl-phosphonate using Horner-Wittig reaction to produce trans-stilbene derivative. The reactions were carried out under nitrogen gas using solvent anhydrous THF. Production of 2, 4, 4'-trimethoxy-stilbene was synthesized using Horner–Wittig reaction only. The reaction was carried out under nitrogen gas and solvent DMF. Final products were characterized by NMR and melting point, which were in full accordance with the depicted structures.

Mechanisms

Mechanism of Wittig Reaction: This mechanism requires the use of a strong base (commonly butyl lithium) to carry out the deprotonation and moister free conditions. Thus, the phosphonium ion is deprotonated by base [34,35]. Phosphorus atom is a strong electron-withdrawing group positively charged and able to activate the neighboring carbon atom as a weak acid [36] (Figure 3). Methoxylated analogues of resveratrol such as *trans* 3,4,5,4'-tetramethoxystilbene (DMU 212) was synthesized using Wittig reaction. Other methoxylated analogues are synthesized using Horner-Wittig reaction such as 2,4,4'-trimethoxy stilbene and 3,4',5- trimethoxy stilbene. The mechanism of Horner-Wittig reaction is similar to Wittig reaction, it is a variation made by Leopold Horner [35-37]. The only difference is Horner-Wittig reaction selectively produces *trans*-formation of stilbene whereas Wittig reaction produces both *trans* and *cis* products.

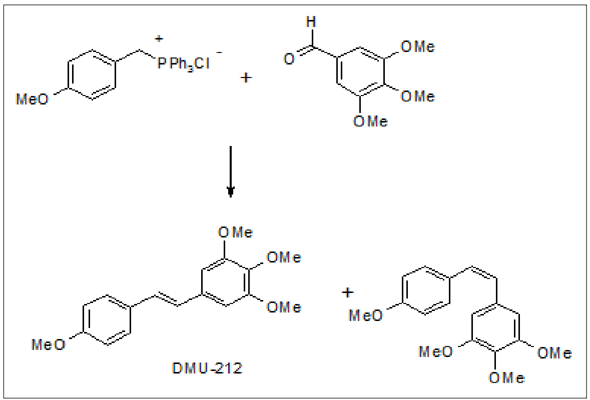

Figure 3: DMU212 synthesis by Wittig reaction.

A General Wittig procedure for synthesis of *trans* and *cis*-stilbenes: (Figure 3) To a stirred suspension of the 4-methoxybenzyltriphenylphosphonium chloride (1.194mmol, 0.5g) in anhydrous THF (20mL), at -20°C, under N_2 was added drop wise a solution of *n*-butyllithium in hexanes (0.78mL, 1.19 mmol, 2.5M). A TLC plate was carried out with the mobile phase of ethyl acetate/hexane (7:3). Reaction mixture is spotted against the starting material on the TLC plate. From the plate no starting material was present in the reaction mixture and Rf values were obtained. The resulting red suspension was stirred for 20min at -20°C and then the 3, 4, 5- trimethoxy benzaldehyde (1.194mmol, 0.23g), in anhydrous THF (10ml) was added drop wise. The reaction was stirred for 1h at -20°C and then allowed to warm to room temperature and stirred overnight.

The reaction mixture was quenched with ice-water (40ml) and extracted with ethyl acetate (3 x 20ml). The combined organic extracts were washed with water (2 x 20ml), brine (2 x 20ml) and dried over anhydrous magnesium sulphate. The solvent was removed in vacuum. The solution was collected from the vacuum and placed in the round bottom flask and attached to the rotary evaporator. Crude product was obtained. Flash column chromatography (petroleum ether/ ethyl acetate 5:5) afforded the *cis*- and *trans*- stilbenes respectively. 3',4,4',5'-tetramethoxystilbene. A cream solid; Yield: 0.7g (30%); mp 157°C; ^{1}H NMR (CDCl3): e 7.44 (d, J = 8.8Hz,2H), 6.98 (d, J = 16.3Hz, 1H), 6.91-6.83 (m, 3H), 6.71 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): e 159.2, 153.3, 137.7, 133.3, 129.9, 127.6, 127.5, 126.4, 114.1, 103.2, 60.9, 56.0, 55.2.

A Horner-Wittig Procedure for synthesis of trans-3,4,4',5'- tetramethoxystilbene (DMU 212): (Figure 4) A mixture of 4-methoxybenzylchloride (6.39mmol/ 3.6ml) and triethylphosphite (7.98mmol/ 5.46ml) was heated to reflux for 3h. A TLC plate was carried out to observe if the reaction had gone to completion. According to the TLC plate there was some starting material present. The reaction mixture was left for a further of five days. Another TLC plate was carried out after five days the reaction had gone to completion. After controlling by thin layer chromatography (TLC: Rf. = 0.17 ethyl acetate/ petroleum ether 2:8) that the reaction was complete, the excess triethylphosphite was removed in vacuo to afford diethyl-4-methoxybenzylphosphonate as viscous straw colored oil. A cooled solution of diethyl-4-methoxybenzylphosphonate (20mmol, 5.06g) in DMF (20ml) was added to the stirred suspension of sodium tert-butoxide (40mmol, 3.84g) in DMF (20ml) at 0°C under N_2. The pale yellow solution was stirred at 0°C for a further 40min.

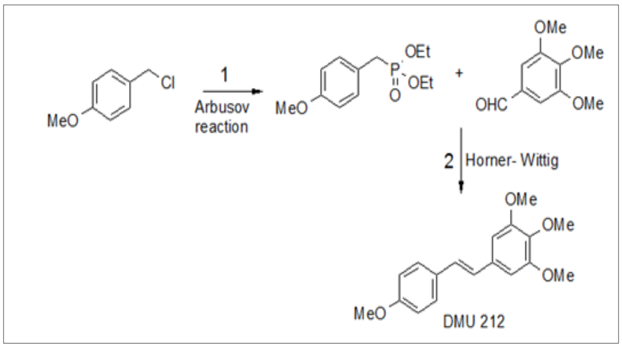

Figure 4: DMU212 synthesis by Horner-Wittig reaction.

A cooled solution of 3,4,5-trimethoxybenzaldehyde (20mmol, 3.92g) in DMF (10ml) was siphoned in the mixture. The resulting pale yellow mixture was stirred for further 1h and then allowed to cool to room temperature over 1.5h. A TLC plate was carried out to ensure reaction has gone to completion. The mixture was heated to 95°C for 20min and then allowed to cool to room temperature. The mixture was quenched with water (50ml) and the white precipitate formed was removed by filtration, washed with water (20ml) and cooled ethanol (20ml). Recrystallization from ethylacetate afforded DMU 212 as white crystalline solid. 3',4,4',5'-tetramethoxystilbene. A white solid; Yield: 3g (76.5%) m.p. 157°C; ^{1}H NMR ($CDCl_3$): H 7.44 (d, J = 8.8Hz,2H), 6.98 (d, J = 16.3Hz, 1H), 6.91-6.83 (m, 3H), 6.71 (s, 2H), 3.90 (s, 6H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$): e 159.2, 153.3, 137.7, 133.3, 129.9, 127.6, 127.5, 126.4, 114.1, 103.2, 60.9, 56.0, 55.2.

Synthesis of Diethyl-4-Methoxybenzylphosphonate: A mixture of 4-methoxybenzylchloride (27.2mmol, 3.69ml) and triethylphosphite (32.7mmol, 5.6ml) was heated to reflux for 3h. A TLC plate was made using mobile phase of ethyl acetate/ petroleum ether (2:8) to observe if the reaction mixture had gone to completion. From the TLC plate, starting material was showed in the reaction mixture. The reaction was left for another three days to go to completion. After controlling by thin layer chromatography (TLC:Rf. = 0.17 ethyl acetate/petroleum ether 2:8) that the reaction was complete, the excess triethylphosphite was removed in vacuo to afford diethyl-4-methoxybenzylphosphonate. Total stock material collected was 5.32g of diethyl-4-methoxybenzylphosphonate.

Horner-Wittig Synthesis of 2,4,4'-Trimethoxystilbene: Figure 5 A cooled solution of diethyl-4-methoxybenzylphosphonate (77mmol, 2g) in DMF (20ml) was added to the stirred suspension of sodium *tert*-butoxide (15.4mmol, 1.48g) in DMF (20ml) at 0°C under N_2. The pale yellow solution was stirred at 0°C for a further 40min. A cooled solution of 2,4-dimethoxybenzaldehyde (77mmol, 1.29g) in DMF (10ml) was siphoned into the mixture. The resulting pale yellow mixture was stirred for further 1h and then allowed to warm to room temperature over 1.5h. A TLC plate was carried out against the diethyl-4-methoxybenzylphosphonate to ensure the reaction had gone to completion. From the TLC plate it showed there was starting material present in the reaction mixture. Therefore, the reaction mixture was left on the ice-bath for further five days.

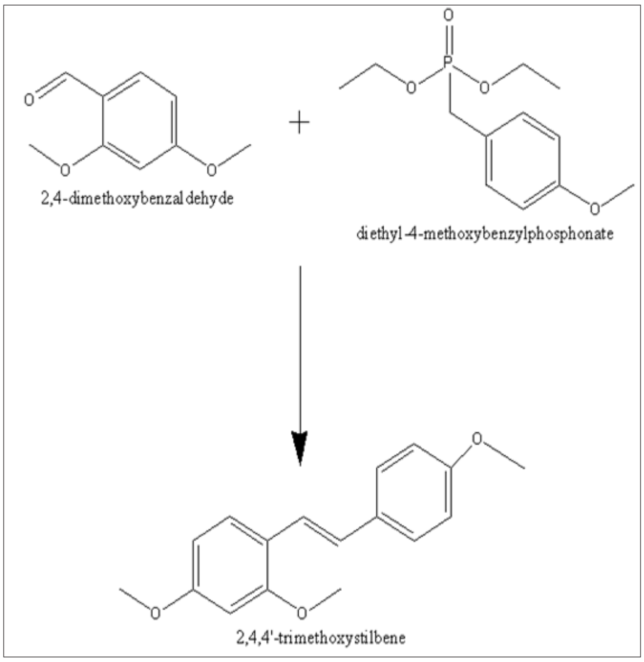

Figure 5: 2,4,4'-trimethoxystilbene synthesis with Horner-Wittig reaction.

Afterwards, another TLC plate was carried out which showed the reaction had gone to completion. The mixture was quenched with water (50ml) and the grey precipitate formed was removed by filtration, washed with water (50ml) and cold ethanol (50ml). The solution was placed on the rotary evaporator to remove the DMF. Recrystallization from ethyl acetate afforded 2,4,4'-trimethoxystilbene. 2,4,4'-trimethoxystilbene. White solid; Yield: 0.56g (43.4%), TLC: Rf. = 0.65 (ethyl acetate/ petroleum ether 1:9); m/z [FAB] 271 [M+1]+, 45%); H (CDCl3) 3.80 (9H, s, 3 x OMe), 6.40 (1H, t, ArH), 6.65 (2H, d, ArH), 6.85 (1H, d, J=16Hz, C=CH), 6.90 (2H, d, ArH), 7.10(1H, d, J=16Hz, C=CH), 7.4(2H, d, ArH); C (CDCl3), 55.37, 55.40, 99.67, 104.38, 113.69, 126.62, 127.86, 128.33, 128.79, 129.97, 139.75,159.45, 161.02; Anal. Calcd $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found C, 75.60; H, 6.67; HRMS found [M+1]+ 271.1329, $C_{17}H_{19}O_3$ requires [M+1]+ 271.1129.

Results and Discussion

Synthesis of *Trans* and *Cis*-Stilbene

The method we used for the synthesis of *Trans* and *cis*-stilbene is the Wittig reaction [35-37]. This reaction is used to form a double bond between the two compounds. The reaction is used in organic synthesis and to obtain *cis* and *Tran's* form of the product. According to a study of Alonso et al. [38], they used nickel nanoparticles to promote Wittig olefination of benzyl alcohols with benzyidene-triphenyl-phosphorane, a new synthesis of resveratrol, DMU-212 and analogues. In this study we used benzyltriphenylphosphonium chloride and *n*-butyllithium which produced a red suspension. The deep red color is an indication of the "Wittig reagent" ylides. The product alkene and phosphonium salt are normally not colored. Thus, Wittig reactions can be monitored by the formation of red color when ylide is made and the disappearance of the color shows that the ylide has reacted and gone to the final product. When the 3,4,5-trimethoxybenzaldehyde was added to the reaction mixture the suspension changed color from red to yellow.

To see if the reaction had gone to completion a TLC plate was carried out by quenching the reaction. TLC plate showed that the reaction needed an hour to complete. Furthermore, the suspension changed color from yellow to cream. After freeze drying and Büchner filtering the solid and liquid product, they were weighed to obtain the yield. *Trans* stilbene was a cream product and the amount obtained from the experiment was 0.08g. The *cis* stilbene appeared as a straw colored oily liquid and the quantity obtained was 0.01g. Using Wittig reaction, *trans* and *cis* form of stilbene were obtained however the yield of both forms were much less than what was predicted. The retention factor (Rf) value were measured and the Rf value of trans and *cis* stilbene was compared to the DMU-212 rf value. Rf value for *trans, cis* and DMU-212 was 0.34, 0.42 and 0.32. The value of *trans* and DMU-212 is similar to each other which proves the *trans*-stilbene is 3,4,4',5-tetramethoxystilbene which is the same as DMU-212. The yield produce for *trans*-stilbene was 16%. We assume that the reason of low yield is due to some of the material lost during the reaction. *Cis* isomer of the stilbene was also produced therefore some of it must be taken up by the *cis*-isomer and reducing the yield for *trans*-isomer. We are tempted to speculate that to improve the yield of the product Heck reaction could be used in the future. Heck reaction is also selective for *trans* isomer and the yield produced by this reaction can be used to compare with the yield produced by Wittig reaction.

Synthesis of *Trans* 3,4,4',5-Tetramethoxystilbene

We elect to use the Horner-Wittig method because this reaction gives a good *trans* selectivity. The diethyl-4-methoxy-benzyl-phosphonate which was used was synthesized earlier. The second half of the reaction was left longer than the actual method. This is because the reaction had not gone to completion as the red suspension was still visible showing that the ylide was formed, present and had not gone to completion in the product as there is not color change spotted. To confirm a stilbene has been formed, a purple spot was visible under the U.V. light indicating the presence of stilbene when carrying out a TLC plate. Rf values were measured from the TLC plate when the reaction had gone to completion which was 0.136 and this value was compared against the literature Rf value which was 0.17. This reaction produced a greater yield, 0.15 g, of *trans* 3,4,4',5-tetramethoxystilbene compared to the general Wittig reaction. The major difference in yield could be possibly because in the general Wittig reaction, *trans* and *cis* isomers were produced whereas in the Horner-Wittig reaction only *trans* isomer was produced. Again, we may argue that in future Heck reaction can be used to compare.

Synthesis of 2,4,4'-Trimethoxystilbene

Horner-Wittig reaction was used as *trans* isomer of the product needs to be obtained. During the reaction a red suspension had been formed and had changed to a grey color, which showed that ylide had been formed and gone to the product due to the disappearance of the red color. When a TLC plate was made a purple spot was shown under the U.V. light stating that stilbene has formed. This methoxylated analogue has not previously been made, therefore it was hard to compare.

Conclusion

Here, resveratrol analogues were designed to improve potency and biopharmaceutical properties of resveratrol itself. The Horner Wittig reaction produced exclusively *trans* stilbene with high yields. To form the alkene bond between the two aromatic rings, Wittig olefination reaction is essential. Wittig reaction requires a phosphonium ylide to form a phosphonium ion, the increase in stability of this ylide will favors *trans* form of stilbene. Non-polar solvents and salt free conditions induce *cis* formation of stilbene due to the diminish of the ylide. The number and position of the methoxy group exerts significant influence on the yield and efficacy of methoxylated resveratrol analogues.

Structural modification of resveratrol by substituting the hydroxyl group with methoxy group on the aromatic ring could possibly have an effect on insulin sensitivity. Indeed, resveratrol has low bioavailability due to being metabolized by sulfation and glucuronation in the liver. Bioavailability can be increased by designing resveratrol analogues which would reduce the activity of hydroxyl group on resveratrol. Methoxylation of hydroxyl groups is supposed to prevent polyphenol metabolism and enhance stilbene bioactivity. Methoxylated analogues of resveratrol possess increased lipophilicity which would increase its bioavailability as it will stay longer in the body rather than getting excreted out of the body. Further studies should be addressed for the effectiveness and efficacy of such new analogues considering the crucial role of resveratrol in some of the most human deleterious diseases [39-42].

Acknowledgement

The authors are grateful to De Montfort University for funding.

References

1. Bhatt JK, Thomas S, Nanjan MJ (2012) Resveratrol Supplementation improves glycemic control in type 2 diabetes mellitus. Nutrition Research 32(7): 537-541.
2. Palsamy P, Subramanian S (2008) Resveratrol, a natural phytoalexin, normalizes hyperglycemia in streptozotocin-nicotinamide induced experimental diabetic rats. Biomedicine and Pharmacotherapy 62(9): 598-605.
3. Borriello A, Cucciolla V, Della Ragione F, Galletti P (2010) Dietary polyphenols: Focus on resveratrol, a promising agent in the prevention of cardiovascular diseases and control of glucose homeostasis. Nutrition Metabolism and Cardiovascular Diseases 20(8): 618-625.
4. (2016) WHO, Global Report on Diabetes World Health Organization, Geneva, USA, p. 1-88.
5. Szkudelska K, Skudelski T (2010) Resveratrol, Obesity and Diabetes. European Journal of Pharmacology 635(1-3): 1-8.
6. (2012) Diabetes in the UK. Key statistics on Diabetes. England, UK.
7. Schmatz R, Perreira LB, Stefanello N, Mazzanti C, Spanevello R, et al. (2012) Effects of resveratrol on biomarkers of oxidative stress and on the activity of delta aminolevlinic acid dehydratase in liver and kidney of streptozotocin-induced diabetic rats. Biochimie 94(2): 374-383.
8. Bagul PK, Middela H, Matapally S, Padiya R, Bastia T, et al. (2012) Attenuation of insulin resistance, metabolic syndrome and hepatic oxidative stress by resveratrol in fructose-fed rats. Pharmacological Research 66(3): 260-268.
9. Zhang J, Chen L, Zheng J, Zeng T, Li H, et al. (2012) The protective effect of resveratrol on islet of insulin secretion and morphology in mice on a high-fat diet. Diabetes Research and Clinical Practice 97(3): 474-482.
10. Szkudelski T (2008) The insulin-suppressive effect of resveratrol - An in vitro and in vivo phenomenon. Life Sciences 82(7-8): 430-435.
11. Gerogiannaki Christpoulou M, Athanasopoulos P, Kyrikidis N, Gerogiannaki IA, Spanos M (2006) *trans*-Resveratrol in wines from the major Greek red and white grape varieties. Food Control 17(9): 700-706.
12. Naderali EK (2009) Obesity and cardiovascular dysfunction: A role for resveratrol? Obesity Research & Clinical Practice 3(1): 45-52.
13. Ding DJ, Cao XY, Dai F, Li XZ, Liu GY, et al. (2012) Synthesis and antioxidant activity of hydroxylated phenanthrenes *cis*-restricted resveratrol analogues. Food Chemistry 135(3): 1011-1019.
14. Likhtenshtein GI (2012) Stilbenes synthesis and application.
15. (2012) Kirk-Othmer Encyclopedia of Chemical Technology. The NHS Information Centre. Statistics on obesity, physical activity and diet: England, Uk, p. 1-24.
16. Sharma S, Misra CS, Arumugam S, Roy S, Shah V, et al. (2011) Antidiabetic Activity of Resveratrol, a known SIRT1 Activator in a Genetic Model for Type-2 Diabetes. Phytotherapy Research 25(1): 67-73.
17. Carter LG, D'Orazio JA, Pearson KJ (2014) Resveratrol and cancer: focus on in vivo evidence. Endocrine-Related Cancer 21(3): R209-R225.
18. Clement MV, Hirpara JL, Chawdhury SH, Pervaiz S (1998) Chemopreventive agent resveratrol, a natural product derived from grapes, triggers CD95 signaling-dependent apoptosis in human tumor cells. Blood 92(3): 996-1002.
19. Tsai SH, Lin Shiau SY, Lin JK (1999) Suppression of nitric oxide synthase and the down-regulation of the activation of NFkB in macrophages by resveratrol. British Journal of Pharmacology 126(3): 673-680.
20. Nakagawa H, Kiyozuka Y, Uemura Y, Senzaki H, Shikata N, et al. (2001) Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator. Journal of Cancer Research and Clinical Oncology 127(4): 258-264.
21. Murakami A, Matsumoto K, Koshimizu K, Ohigashi H (2003) Effects of selected food factors with chemopreventive properties on combined lipopolysaccharide- and interferon-g-induced IkB degradation in RAW264.7 macrophages. Cancer Letters 195(1): 17-25.
22. Garvin S, Ollinger K, Dabrosin C (2006) Resveratrol induces apoptosis and inhibits angiogenesis in human breast cancer xenografts *in vivo*. Cancer Letters 231(1): 113-122.

23. Kalra N, Roy P, Prasad S, Shukla Y (2008) Resveratrol induces apoptosis involving mitochondrial pathways in mouse skin tumorigenesis. Life Sciences 82(7-8): 348-358.
24. Subbaramaiah K, Chung WJ, Michaluart P, Telang N, Tanabe T, et al. (1998) Resveratrol inhibits cyclooxygenase-2 *trans*cription and activity in phorbol ester-treated human mammary epithelial cells. Journal of Biological Chemistry 273(34): 21875-21882.
25. Jang M, Pezzuto JM (1999) Cancer chemopreventive activity of resveratrol. Drugs Under Experimental and Clinical Research 275: 65-77.
26. MacCarrone M, Lorenzon T, Guerrieri P, Agro AF (1999) Resveratrol prevents apoptosis in K562 cells by inhibiting lipoxygenase and cyclooxygenase activity. European Journal of Biochemistry 265(1): 27-34.
27. Holmes McNary M, Baldwin ASJr (2000) Chemopreventive properties of *trans*-resveratrol are associated with inhibition of activation of the Ikappa B kinase. Cancer Res 160(13): 3477-3483.
28. Benitez DA, Hermoso MA, Pozo-Guisado E, Fernandez Salguero PM, Castellon EA (2009) Regulation of cell survival by resveratrol involves inhibition of NF kappa B-regulated gene expression in prostate cancer cells. Prostate 69(10): 1045-1054.
29. Csaki C, Mobasheri A, Shakibaei M (2009) Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. Arthritis Res Ther 11(6): R165.
30. Dawson MA, Kouzarides T (2012) Cancer epigenetics: from mechanism to therapy. Cell 6 150(1): 12-27.
31. Gaukroger K, Hadfield JA, Hepworth LA, Lawrence NJ, McGown AT (2001) Novel Syntheses of *Cis* and *trans* Isomers of Combretastatin A-4. J Org Chem 66(24): 8135-8138.
32. Kang SS, Cuendent M, Endringer DC, Croy VL, Pezzuto JM, et al. (2009) Synthesis and biological evaluation of a library of resveratrol analogues as inhibitors of Cox-1, Cox-2 and NF-KB. Bioorganic and Medicinal Chemistry 17(3): 1044-1054.
33. Hong B, Ding X, Jia H, Zhang J (2017) Resveratrol ameliorated gestational diabetes through regulation of AMPKmediated NF-kB signaling pathway. Biomedical Research 28(8): 3433-3439.
34. Huang JP, Huang SS, Deng JY, Chang CC, Day YJ, et al. (2010) Insulin and resveratrol act synergistically, preventing cardiac dysfunction in diabetes, but the advantage of resveratrol in diabetics with acute heart attack is antagonized by insulin. Free Radical Biology and Medicine 49(11): 1710-1721.
35. Craig P, Jasperse CP (2013) Wittig Reaction. Minnesota State University, USA.
36. Burkhardt K (2012) Horner-Wittig Reaction: Synthesis of 1,4 diphenyl-1,3-butadiene. Institute of Technology, Georgia.
37. Horner L, Hoffmann HMR, Wippel HG (1958) Über Triphenyl-phosphin-methylene als olefinbildende Reagenzien I. Chemische Berichte 91: 61-63.
38. Alonso F, Riente P, Yus M (2009) Synthesis of resveratrol, DMU-212 and analogues through novel Wittig-type olefination promoted by nickel nanoparticles. Tetrahedron Letters 50(25): 3070-3073.
39. Yun JM, Chien A, Jilal I, Devaraj S (2012) Resveratrol up-regulates SIRT1 and inhibits cellular oxidative stress in the diabetic milieu: mechanistic insights. Journal of Nutritional Biochemistry 23(7): 699-705.
40. Liu C, Yen H, Tsao C, Su HY, Lin YW (2017) Resveratrol inhibits ovarian cancer cell growth through epigenetic regulation of Wnt antagonist SFRP5. The FASEB Journal 31 Supplement 790.10.
41. Zhang B, Lakshmanan J, Motameni A, Harbrecht BG (2017) Resveratrol-Mediated Repression of a Liver Cancer Cell Line. The FASEB Journal 31(1): 1067.5.
42. León D, Uribe E, Zambrano A, Salas M (2017) Implications of Resveratrol on Glucose Uptake and Metabolism. Molecules 7: 22(3).

This work is licensed under Creative Commons Attribution 4.0 License

Submission Link: https://biomedres.us/submit-manuscript.php

Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

https://biomedres.us/